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EXAMINER	
HAMA, JOANNE	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/622,377	JENTSCH, THOMAS J.	
	Examiner	Art Unit	
	Joanne Hama, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-41* is/are pending in the application.

4a) Of the above claim(s) *31-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *7/18/03* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/13/04;5/18/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Application, filed July 18, 2003, is a continuation of CT/DK/02/00038, filed January 17, 2002. This Application claims benefit to German (DE) Patent Application 101 02 977.2 filed on January 23, 2001.

Claims 26-41 are pending.

Election/Restrictions

Applicant's election with traverse of Group I (claims 26-30) in the reply filed on March 11, 2005 is acknowledged. The traversal is on the ground(s) that there will be no undue burden imposed by examination of multiple groups, especially if groups are classified in the same class and/or subclass. Further, the Applicant points out that, the cell lines of Group I are, in fact, the same cell lines used in the inventions of Group III and IV. The Examiner has considered the Applicant's arguments and agrees with the fact that because Group III and IV depend on Group I, they should be examined together. For this reason, Groups I, III, and IV will be combined in this examination. Claim 31, directed to the genetically modified animal and claim 41, directed to use of substances which inhibit chloride channels remain restricted from the cell lines and their method of use. Claims 31 and 41 remain separate from Claims 26-30, 32-40, as they are materially different from cells. Further, the methods in used in obtaining cells are materially different from those used in making a transgenic animal. Also, the methods

used in making substances that inhibit chloride channels is different from those used to make cells and a transgenic animal.

Claims 31, 41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Groups, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on March 11, 2005.

As the Groups I, III, and IV have been combined, the new assignment of groups and their claims are as follows:

Group I (claims 26-30, 32-40), drawn to a cell line which does not express or expresses to a reduced extent one or more chloride channels and use of the cell lines in a screen for compounds.

Group II (claim 31), drawn to a genetically modified non-human mammal, wherein the coding sequence of ClC-7 in the non-human mammal is modified.

Group III (claim 41), drawn to use of substances which completely or partially inhibit the ClC-7.

Claims 26-30, 32-40, drawn to a cell line which does not express or expresses to a reduced extent one or more chloride channels and use of a cell line which does not express or expresses to a reduced extent one or more chloride channels, are under consideration.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Germany on January 23, 2001. It is noted, however, that applicant has not filed a certified copy of the 10102977.2 application as required by 35 U.S.C. 119(b).

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered. The specification on pages 15-24 comprises a list of references. If these references are to be considered, they must be listed on an IDS and copies of the references must be submitted.

References C9, C55, and C90 are duplicate citations of references (IDS, filed May 18, 2004). They have been indicated as "dup" and have been crossed off the IDS.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 32-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 32-37 provides for the use of a cell line, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 32-37 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claims 26, 29, 30, 38-40 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

When determining whether an applicant has described the utility of an invention, one has to determine whether the applicant has described a well-established utility. If not, has the application made any assertion of specific, substantial, and credible utility. A credible utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for use. In contrast to general utility, a specific utility will be specific to the claimed subject

matter. A substantial utility defines a "real world" utility of the invention and utilities that require or constitute carrying out further identify or reasonably confirm a real world context use are not substantial utility (see utility guidelines, in Federal Register, January 5, 2001, Volume 66, Number 5, pages 1092-1099).

When the claims are analyzed in light of the specification, the instant invention encompasses:

a cell line comprising a loss of expression or reduction of expression of ClCl-4,

a cell line that expresses ClC-4, but not ClC-3, ClC-6, ClC-5, and ClC-7

a cell line comprising a loss of expression or reduction of expression of ClC-6, and

a cell line that expresses ClC-6, but not ClC-3, ClC-4, ClC-5, and ClC-7.

In order for one to analyze utility of the claimed invention, it is asked if the proteins, ClC-4 and ClC-6, have an established and specific biological function.

With regards to the instant invention encompassing a cell line comprising a loss of expression or reduction of expression of ClC-4 and a cell line that expresses ClC-4, but not ClC-3, ClC-6, ClC-5, and ClC-7, neither cell line is considered to have a specific and substantial utility. At the time of filing, the art teaches that ClC-4 has a sequence similar to ClC-3 and ClC-5 (Jentsch, et al., 1999, Pflugers Arch—Eur. J. Physiology, 437: 783-795; page 789, 1st col, lines 3-4) and the art teaches that stably transfected CHO cells expressing hClC-4sk demonstrated a rectifying current when the pH was changed from 7.2 to 4.5 (Kawasaki et al. 1999, Am. J. Physiol., (Cell Physiol. 46) 277:

C948-C954). However, neither the specification nor the art teach what the biological function of ClC-4 is, (i.e. what role it has in the organism). It is emphasized that the CHO cell assay, which demonstrated a rectifying current does not demonstrate a specific activity of ClC-4. Rather, it is a general assay for chloride channels and cannot be used to distinguish chloride channels from each other. As such, the art teaches that the chloride family is divergent and the channels perform different functions. These functions include the control of electrical excitability, transepithelial transport, and the charge compensation necessary for the acidification of intracellular organelles. In addition, CLC channels may play a role in cell volume regulation (Jentsch, et al., 1999, Pflugers Arch—Eur. J. Physiology, 437: 783-795; page 783, 2nd col., 2nd parag., lines 1-6). Nothing in the specification indicates that ClC-4 has any of these functions, or any newly identified function. Therefore, the specification does not teach that ClC-4 has a biological activity, explicitly or implicitly as considered by the specification. There is no teaching of any assay method for assaying the function of ClC-4. It is emphasized that the CLC family is diverse (Jentsch, et al., 1999, Pflugers Arch—Eur. J. Physiology, 437: 783-795 demonstrates a dendrogram indicating the degree of similarity between different CLC gene products, Figure 1) and the biological functions of the CLC family are diverse. In other words, the only immediate apparent utility for the instant invention would be its further scientific characterization as a putative CLC. Finally, the specification does not provide any evidence as to what diseases the claimed polynucleotide or encoded protein is related to. In the absence of such a disclosure, it is unclear what diseases could be treated with the candidate thereapeutic compounds

identified by the claimed method and if no such relationship of a disease with the protein of the claimed invention is known what will be the utility of the compounds.

Therefore, the asserted use for the claimed cells is not considered to be supported by either a specific and substantial utility since no function can be ascribed to ClC-4.

With regards to the instant invention encompassing a cell line comprising a loss of expression or reduction of expression of ClC-6, and a cell line that expresses ClC-6, but not ClC-3, ClC-4, ClC-5, and ClC-7, neither cell line is considered to have a specific and substantial utility. While the art teaches that ClC-6 has the structure of a chloride channel (Brandt and Jentsch, 1995, FEBS Letters, 377: 15-20, page 18, 2nd col., 3rd parag., see also Figure 2) and electrophysiology studies demonstrated that ClC-6, when expressed in Xenopus oocytes, has a outwardly-rectifying current and inactivated slowly at positive potentials (Buyse, et al., 1997, JBC, 272: 3615-3621, page 3618, 1st col., 2nd parag., lines 1-5), neither the specification nor the art teach what the biological function of ClC-6 is, (i.e. what role it has in the organism). It is emphasized that the Xenopus oocyte assay, which demonstrated a rectifying current does not demonstrate a specific activity of ClC-6. Rather, it is a general assay for chloride channels and cannot be used to distinguish chloride channels from each other. As such, the art teaches that the chloride family is divergent and the channels perform different functions. These functions include the control of electrical excitability, transepithelial transport, and the charge compensation necessary for the acidification of intracellular organelles. In

addition, CLC channels may play a role in cell volume regulation (Jentsch, et al., 1999, Pflugers Arch—Eur. J. Physiology, 437: 783-795; page 783, 2nd col., 2nd parag., lines 1-6). Nothing in the specification indicates that ClC-6 has any of these functions, or any newly identified function. Therefore, the specification does not teach that ClC-6 has a biological activity, explicitly or implicitly as considered by the specification. There is no teaching of any assay method for assaying the function of ClC-6. It is emphasized that the CLC family is diverse (Jentsch, et al., 1999, Pflugers Arch—Eur. J. Physiology, 437: 783-795 demonstrates a dendrogram indicating the degree of similarity between different CLC gene products, Figure 1) and the biological functions of the CLC family are diverse. In other words, the only immediate apparent utility for the instant invention would be its further scientific characterization as a putative CLC. Finally, the specification does not provide any evidence as to what diseases the claimed polynucleotide or encoded protein is related to. In the absence of such a disclosure, it is unclear what diseases could be treated with the candidate therapeutic compounds identified by the claimed method and if no such relationship of a disease with the protein of the claimed invention is known what will be the utility of the compounds.

Therefore, the asserted use for the claimed cell is not considered to be supported by either a specific and substantial utility since no function can be ascribed to ClC-6.

Claims 26, 29, 30 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and

substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26-30, 32-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a cell line comprising a disruption in its endogenous ClC-1, ClC-2, ClC-Ka, ClC-Kb, ClC-3, ClC-5, and/or ClC-7 gene of the mouse genome, wherein in there is no expression of functional ClC-1, ClC-2, ClC-Ka, ClC-Kb, ClC-3, ClC-5, and/or ClC-7 from the endogenous gene,

does not reasonably provide enablement for:

a cell line comprising a loss of expression or reduction of expression of ClCl-4,

a cell line that expresses ClC-4, but not ClC-3, ClC-6, ClC-5, and ClC-7

a cell line comprising a loss of expression or reduction of expression of ClC-6, and

a cell line that expresses ClC-6, but not ClC-3, ClC-4, ClC-5, and ClC-7.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

In addition to the issues raised in the utility rejection regarding ClC-4 and ClC-6, the claimed invention is not enabled for the reasons set forth below. If the utility rejection was to be withdrawn, these rejections would remain.

When the claims regarding ClC-4 and ClC-6 are analyzed in light of the specification, the instant invention encompasses

a cell line comprising a loss of expression or reduction of expression of ClCl-4,

a cell line that expresses ClC-4, but not ClC-3, ClC-6, ClC-5, and ClC-7

a cell line comprising a loss of expression or reduction of expression of ClC-6, and

a cell line that expresses ClC-6, but not ClC-3, ClC-4, ClC-5, and ClC-7,

and methods of using said cell lines in a screen to identify substances which are suitable for inhibiting one or more chloride channels, including ClC-4 and ClC-6.

As discussed in the utility rejection, there is no guidance and evidence in the specification as to what the biological function is of ClC-4 and ClC-6, how to test the biological functions of ClC-4 and ClC-6, which disease the protein's expression is related to, and how to screen for compounds that inhibit ClC-4 and ClC-6. The art teaches that the CLC family of proteins is diverse and the family members perform different biological functions (Jentsch, et al., 1999, Pflugers Arch—Eur. J. Physiology, 437: 783-795, see page 783, 2nd col., 2nd parag., lines 1-6 and Figure 1). Additionally, the art does not teach which disease(s) ClC-4 and ClC-6 is associated with. Thus, it stands that an artisan has to establish the relationships between ClC-4 and a disease and ClC-6 and a disease before cells comprising expression of ClC-4, but not ClC-3, ClC-5, ClC-6, ClC7 and cells comprising expression of ClC-6, but not ClC-3, ClC-4, ClC-5, ClC-7 can be used in a screen for therapeutics.

With regards to using the cells comprising expression of ClC-4, but not ClC-3, ClC-5, ClC-6, ClC7 and cells comprising expression of ClC-6, but not ClC-3, ClC-4, ClC-5, ClC-7 in a method for identifying substances which inhibit ClC-4 and ClC-6, the specification as filed does not teach any assays that monitor the biological function of

ClC-4 or ClC-6. As such, an artisan would not know how to screen for compounds if no guidance is taught as to what biological function is monitored.

Therefore, an artisan would have to carry out extensive experimentation to first characterize ClC-4 and ClC-6 to determine its relationship to a biological function, establish an assay system to detect the activity of ClC-4 and ClC-6, and determine a relationship of the ClC-4 and ClC-6 to a phenotype before it can be used for screening of candidate therapeutic compounds. Such experimentation would be undue since neither the art nor the specification provides any guidance.

Accordingly, in view of the quantity of experimentation necessary to establish a biological function of ClC-4 and ClC-6, to establish its relationship to a disease, and to establish an assay system to determine its biological activity, the lack of direction or guidance provided by the specification, and the absence of working examples with regards to the method claimed, it would have required undue experimentation of one skilled in the art to use the claimed invention.

In addition to the enablement issues addressed for cells comprising ClC-4, but not ClC-3, ClC-6, ClC-5, and ClC-7 and cells comprising ClC6 but not ClC-3, ClC-4, ClC-5, and ClC-7, other enablement issues are directed to claim 26, which broadly claims "a cell line which does not express or express only to a reduced extent one or more chloride channels from the group consisting of ClC-1, ClC-2, ClC-1, ClC-Ka, ClC-Kb, ClC-3, ClC-4, ClC-5, ClC-6, and ClC-7." Claims 27-30 depend on claim 26.

With regards to a cell line which does not express or expresses to only a reduced extent one or more chloride channels, this encompasses cell lines that express RNAi, ribozymes, and antisense RNA. At the time of filing, the specification does not teach an artisan how to make RNAi, ribozymes, and antisense which specifically target chloride channels, thereby reducing their expression. At the time of filing, the use of RNA molecules such as RNAi, ribozymes, and antisense RNA to predictably and routinely effect a biological change is not known in the art. Rather there have been many examples where the introduction of RNA molecules for purposes of gene therapy have resulted in unexpected results. For example, a review by Agrawal and Kanimalla (2000, Molecular Medicine Today, 61: 72-81) teaches that the use of antisense as a means of targeting a gene is unpredictable. "A good part of nucleotide design for its target RNA varies significantly, depending on base composition and sequence. Therefore, the antisense activity of a selected oligonucleotide is influenced both by its base composition and by its sequence. Introduction of oligonuclotides that contain certain sequence motifs, such as CpG and GGGG (hyper-structure-forming sequences) induce cell proliferation and immune responses.... If an antisense oligonuclotide possess self-complementarity or a palindromic sequence, it can form stable secondary structures such as short linear duplexes or hairpins. In such cases, secondary structure formation competes for binding to the target mRNA. In addition, these secondary structures can serve as decoys by binding to cellular factors, thereby inhibiting or inducing the functions of non-targeted genes, which could directly or indirectly alter the function of the gene being studied (page 77, second column, "Choice of oligonucleotide

sequences," first and second paragraphs)." Thus, because not all antisense constructs will function as predicted, all antisense constructs need to be tested for function and efficacy. The specification does not provide any examples of antisense constructs that were able to reduce the expression level of a target gene and thus does not enable one skilled in the art to make and/or use a plasmid vector expressing therapeutic RNA in the treatment of an animal. While Agrawal and Kanimalla teach that designing antisense molecules are unpredictable as described above, it should be pointed out that for similar reasons, the making of RNAi and ribozymes are unpredictable as well.

With regards to a cell line which does not express or expresses to only a reduced extent one or more chloride channels, this encompasses cell lines in which the regulatory regions of chloride channels are altered such that the expression of mRNA encoding a chloride channel is reduced or absent from a cell. At the time of filing, the art teaches that identifying regulatory regions in promoters was unpredictable. For example, Goswami et al. (2003, Journal of Molecular Evolution, 57:44-51) teach some of the analyses used to characterize a promoter. Goswami et al. show by 5' deletion analysis that BD2, a greater 5' deletion of the TGF-β5 promoter than BD3, has more activity than BD3, suggesting that the 5' deletion in BD2 uncovered a negative regulator in the promoter (page 46, column 2, first paragraph, lines 3-7). Goswami et al. also show that while there is this difference in promoter activity between the two constructs transfected in XTC cells (*Xenopus* tadpole cell line), there is no difference in the activity of the promoters when transfected in A6 cells (*Xenopus* adult kidney fibroblast cell line). This result suggests that there is a difference in the transcriptional factors between the

cell types (page 46, column 2, first paragraph, lines 7-10). Goswami et al. also show that there is a difference in promoter regulation, depending what animal species that promoter is from and into which cells the reporter construct is transfected. TGF-β5, which is found in rats and frogs, was found to be regulated differently. *Xenopus* TGFβ-5 transfected into *Xenopus* cells had activity; it had little to no activity when transfected into mammalian cells (page 47, column 2, section headed "Basal Promoter Activites of TGFβ1 and TGF-β5 Promoter in Mammalian Cell Lines", see also Figures 3 and 4). In applying the teachings of Goswami et al. to the instant application, the specification does not teach how to predictably obtain a promoter that regulates a chloride channel's mRNA expression and alter it such that the expression driven from the promoter is less than what it was originally. The specification does not teach what regulators comprise any of the chloride channels' promoters (i.e. negative or positive regulators), such that deletion of the positive regulators results in downregulation of gene expression. As such because identifying where and what the regulators are in a promoter is unpredictable and is done empirically, obtaining any chloride channel promoter without guidance on how to alter it to express little to no chloride channel transcript would be undue experimentation.

Claims 32-40 are to methods for identifying and testing of substances which inhibit ClC-7, ClC-3, ClC-4, and ClC-6, wherein identifying and testing is carried out on the claimed cells. As described above, for reasons of utility and enablement, an artisan does not know how to use any cell comprising ClC-4 and any cell comprising ClC-6, in a

method for testing and identifying a substance that inhibits ClC-4 or ClC-6. Thus, claims 35, 36, and 37 (as it reads on ClC-4 and ClC-6) will be excluded from this part of the analysis regarding a method of testing and identifying a compound.

The art and the specification enables an artisan to use an osteoclast cell line which expresses ClC-7, but not ClC-3,ClC-4, ClC-5, and ClC-6 and a hippocampal cell line which expresses ClC-3, but not ClC-4, ClC-5, ClC-6, and ClC-7. With regards to claim 33, the Examiner has interpreted the claim to read that the cell used in a method for identifying and testing substances that treat osteoporosis of Paget's disease, is an osteoclast cell line which expresses ClC-7, but not ClC-3, ClC-4, ClC-5, treated with a substance that inhibits ClC-7. If this is the case, then the osteoclasts have little to no active ClC-7 and would behave in a manner similar to osteoclasts in knockout ClC-7 mice. The knockout ClC-7 mice exhibit osteopetrosis (thickened sclerotic bones, resulting from deposition of bone and reduced loss of bone) and not osteoporosis (bone loss) or Paget's disease (a disease wherein the bone breaks down more quickly than grows). Osteoporosis and Paget's disease, symptom-wise, are opposite to osteopetrosis. Nothing in the art or the specification teaches how to use an osteoclast cell line which expresses ClC-7, but not ClC-3, ClC-4, ClC-5 to screen for substances which could alleviate bone loss. Without guidance as to how an artisan would perform this screen is undue experimentation.

With regards to claim 37, wherein an osteoclast cell line which expresses ClC-7, but not ClC-3, ClC-4, ClC-5, and ClC-6 and a hippocampal cell line which expresses ClC-3, but not ClC-4, ClC-5, ClC-6, and ClC-7, is used to screen for psychotropic

pharmaceuticals, nothing in the art of the specification teaches that an osteoclast has a role in controlling emotions. In addition to this, nothing in the art or the specification teaches that ClC-3 has a role in an area of the brain that controls emotions. With regards to whether a hippocampal cell line which expresses ClC-3, but not ClC-4, ClC-5, ClC-6, and ClC-7 can be used in a method to screen for compounds suitable for psychotropic pharmaceuticals, the art teaches that depression can result from glutamate-induced exocitotoxicity in the hippocampus. For this reason, the specification and the art enable an artisan to practice a method of screening for a psychotropic pharmaceutical using a hippocampal cell line which expresses ClC-3, but not ClC-4, ClC-5, ClC-6, and ClC-7.

Thus, the specification, while being enabling for:

a cell line comprising a disruption in its endogenous ClC-1, ClC-2, ClC-Ka, ClC-Kb, ClC-3, ClC-5, and/or ClC-7 gene of the mouse genome, wherein in there is no expression of functional ClC-1, ClC-2, ClC-Ka, ClC-Kb, ClC-3, ClC-5, and/or ClC-7 from the endogenous gene,

does not reasonably provide enablement for:

a cell line comprising a loss of expression or reduction of expression of ClCl-4,

a cell line that expresses ClC-4, but not ClC-3, ClC-6, ClC-5, and ClC-7

a cell line comprising a loss of expression or reduction of expression of ClC-6, and

a cell line that expresses ClC-6, but not ClC-3, ClC-4, ClC-5, and ClC-7.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 26 is to a cell line which does not express or expresses to only a reduced extent one or more chloride channels from the group consisting of ClC-1, ClC-2, ClC-Ka, ClC-Kb, ClC-3, ClC-4, ClC-5, ClC-6, ClC-7.

Claims 26 is rejected under 35 U.S.C. 102(b) as being anticipated by Matsumura et al. (1999, Nature Genetics, 21: 95-98, see IDS).

Matsumura et al. teach that Clcnk1-/- (wherein the human homolog is ClC-Ka) mice were generated using homologous recombination in embryonic stem cells (Matsumura et al., page 95, 2nd parag. 1st parag. following the Abstract). Embryonic stem cells are used to generate knockout mice are obtained from cell lines. Thus, Matsumura et al. anticipate claim 26.

Claim 26 is rejected under 35 U.S.C. 102(a) as being anticipated by Piwon et al (2000, Nature, 408: 369-373, see IDS).

Piwon et al. teach that ClC-5-/- mice were generated using homologous recombination in embryonic stem cells (Piwon et al., page 373, under "Generation of clcn5- mice"). Embryonic stem cells are used to generate knockout mice are obtained from ES cell lines. Thus, Piwon et al. anticipate claim 26.

Claim 26 is rejected under 35 U.S.C. 102(b) as being anticipated by Lupo et al. (1997, JBC, 272: 31641-31647).

Lupo et al. teach that NIH3T3 cells were treated with actinomycin D, a specific inhibitor of RNA polymerase II (Lupo et al., page 31643, 1st col., 1st parag. under "Effects of Actinomycin D and Cycloheximide on Aldolase A L- and F-type mRNA Expression," lines 1-6). Treatment of the cell line NIH3T3 with actinomycin D inhibits RNA polymerase II. This means that transcription for all genes is inhibited when cells are treated with actinomycin D. This includes transcription of the chloride channels. Thus, Lupo et al. anticipate claim 26.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gronemeir et al. (1994, JBC, 269: 5963-5967, see IDS) in view of Capecchi (1989, Science, 244: 1288-1292) and Alberts et al.(1994, Molecular Biology of the Cell, Garland Publishing: New York, 3rd ed.).

Gronemeier et al. teach that the ADR mouse is a model for human myotonia. The adr allele arose by insertion of a retroposon into the chloride channel gene ClC-1 (Gronemeier, et al., Abstract, lines 8-10). Gronemeier et al. also teach that the chloride channel ClC-1 is necessary for the stabilization of the resting potential in mature vertebrate muscle (Gronemeier, et al, Abstract, lines 1-3).

While Gronemeier et al. teach a mouse comprising a disruption in ClC-1, they do not teach a cell line comprising a disruption in ClC-1.

With regards as to why an ordinary artisan would want to obtain a cell line, Capecchi teaches that one advantage to carrying out in vitro studies over in vivo studies is that many biological questions can be answered directly and more simply with tissue culture systems (Capecchi, page 1288, 3rd parag., lines 3-4).

The generation of a cell line is well known in the art. For example, Alberts et al. teaches that wile most vertebrate cells die after a finite number of divisions in culture, some cells in culture will undergo a genetic change that makes them effectively immortal. Such cells will proliferate indefinitely and can be propagated as a cell line (Alberts et al. page 160, 1st parag. under "Eucaryotic Cell Lines Are a Widely Used Source of Homogenous Cells"). Alberts also teaches that cell lines can be propagated

from cancer cells. Cancer cells differ from those prepared from normal cells. For example, cancer cell lines often grown without attaching to a surface and they proliferate to a very much higher density in a culture dish. Similar properties can be experimentally induced in normal cells by transforming them with a tumor-inducing virus or chemical (Alberts et al., page 160, 2nd parag. under "Eucaryotic Cell Lines Are a Widely Used Source of Homogenous Cells").

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to generate a cell line from an ADR mouse comprising a disruption in CIC-1.

One having ordinary skill in the art would have been motivated to generate a cell line from an ADR mouse in order to use the cell in a screen that identify substances that rescue a cell from the phenotypes caused by CIC-1 disruption. Capecchi teaches that many biological questions can be answered directly and more simply with tissue culture systems.

There would have been a reasonable expectation of success given Gronemeier et al for teaching an ADR mouse comprising a disruption in CIC-1, wherein the mouse exhibits a muscle phenotype and Alberts et al. for teaching how to obtain a cell line from a primary culture.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Blaisdell et al., (1999, Am. J. Respir. Cell Mol. Biol., 20: 842-847) in view of Chalaka et al. (1999, Am. J. Physiol., 277 (Lung Cell. Mol. Physiol. 21): L197-L203) and Capecchi (1989, TIG, 5: 70-76).

Blaisdell et al. teach that when primary fetal distal lung epithelial cells were treated with keratinocyte growth factor (KGF), the mRNA and protein expression of CIC-2 increased in the cells (Blaisdell, page 845, 2nd col., 1st parag. under "Discussion"). Blaisdell et al. teach that KGF leads to fluid accumulation in fetal mouse lung explants and that the fluid expansion of the developing lung occurs by accumulation of chloride and water in the airways (Blaisdell, et al., page 846, 1st col., 1st parag., lines 1-3). Blaisdell et al. teach that non-CFTR chloride secretion exists in the developing fetal lungs because CFTR is not essential for normal lung morphogeneisis (Blaisdell, page 826, 1st col., 2nd parag., lines 1-3). Blaisdell et al. teach that KGF expression in the fetal lung epithelium contributes to fetal lung fluid expansion. Blaisdell et al. teach that aberrant signaling of KGF or an altered regulation of CIC-2 could result in congential malformations of the lung in newborns by affecting pulmonary fluid distension (Blaisdell et al., page 846, 2nd col., 3rd parag., lines 5-12)

While Blaisdell et al. teach a that CIC-2 protein and mRNA expression increases in lung epithelial cells when induced with KGF, they do not teach a fetal lung epithelial cell line comprising a disruption in CIC-2.

A fetal lung cell line is well known in the art. Chalaka et al. teach that a rat pre-type II cell line, FD18 was obtained from rat fetal lungs at gestational days 18-19 and

immortalized with the adenoviral 12S E1A gene product (Chalaka et al., page L197, 1st col., 1st parag. under "Material and Methods, Cell Culture").

Capecchi teaches a method wherein targeted disruption of a gene of interest can be achieved via homologous recombination. Capecchi teaches the parameters used to increase an artisan's chances of performing homologous recombination, which includes, "the frequency of recombination between co-introduced DNA molecules is roughly proportional to the extent of homology between them. When DNA molecules share more than 5 kilobases of homology, then nearly every molecule introduced into the cell nucleus participates in at least one recombination event....DNA ends stimulate the reaction. The ability to mediate homologous recombination is dependent on the cell's postion in the cell cycle, showing a peak of activity in early S phase (Cappechi, page 71, 1st col., 1st parag.)."

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to generate a rat fetal lung cell line comprising a disruption in ClC-2.

One having ordinary skill in the art would have been motivated to generate a fetal rat lung cell line comprising a disruption in ClC-2 in order to obtain a fetal lung cell line that can be used to demonstrate the necessary role of ClC-2 in fetal lung development.

There would have been a reasonable expectation of success given the teachings of Blaisdell et al for demonstrating that KGF upregulates ClC-2 expression in primary cultures of fetal lung cells of rats, that ClC-2 is an ideal candidate chloride channel that

has a role in regulating the fluid expansion of the developing lung, and the teachings of Chalaka et al. for demonstrating a fetal rat lung epithelia cell line was made and immortalized with the adenoviral 12S E1A gene product, and Capecchi for demonstrating that homologous recombination is a method that can be used to generate a disruption in a gene of interest.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Simon et al. (1997, Nature Genetics, 17: 171-178) in view of Capecchi (1989, Science, 244: 1288-1292) and Alberts et al.(1994, Molecular Biology of the Cell, Garland Publishing: New York, 3rd ed.).

Simon et al. teach that disruption of the CLCNKB (also known as ClC-Kb) gene in the genome of humans result in patients exhibiting hypokalaemia, elevated serum bicarbonate levels, salt-wasting, and dehydration (Simon et al., page 175, 2nd col., 1st parag. under "Physiological and Clinical Features," lines 1-12). Simon et al. teach that the mechanism of the defect responsible for the symptoms exhibited by the patients is a failure of normal transit of chloride across the basolateteral membrane into the bloodstream (Simon, et al., page 176, 2nd col., 2nd parag., lines 5-7). Simon et al. teach the physiology of sodium chloride reabsorption in the renal thick ascending limb of Henle's loop in the kidney, (Simon et al, Figure 6b).

While Simon et al teach humans comprising a disruption in ClC-1, they do not teach a cell line comprising a disruption in ClC-1.

Capecchi generally teaches a method for performing homologous recombination. In addition to teaching that the method can be applied to generate a mouse comprising a disruption in the gene of interest in the mouse's genome, Capecchi teaches that the method of targeted gene disruption can be applied to cultured cells in vitro. Capecchi teaches that one advantage to carrying out in vitro studies over in vivo studies is that many biological questions can be answered directly and more simply with tissue culture systems (Capecchi, page 1288, 3rd parag., lines 3-4).

The generation of a cell line is well known in the art. For example, Alberts et al. teaches that wile most vertebrate cells die after a finite number of divisions in culture, some cells in culture will undergo a genetic change that makes them effectively immortal. Such cells will proliferate indefinitely and can be propagated as a cell line (Alberts et al., page 160, 1st parag. under "Eucaryotic Cell Lines Are a Widely Used Source of Homogenous Cells"). Alberts also teaches that cell lines can be propagated from cancer cells. Cancer cells differ from those prepared from normal cells. For example, cancer cell lines often grown without attaching to a surface and they proliferate to a very much higher density in a culture dish. Similar properties can be experimentally induced in normal cells by transforming them with a tumor-inducing virus or chemical (Alberts et al., page 160, 2nd parag. under "Eucaryotic Cell Lines Are a Widely Used Source of Homogenous Cells").

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to generate a cell line obtained from the renal

thick ascending limb of a patient comprising a disruption in his/her CLC-NKB gene in his/her genome.

One having ordinary skill in the art would have been motivated to generate a cell line from the renal thick ascending limb in a human CLC-NKB patient in order to use the renal cell in a study that would elucidate the physiological and biological function of that cell. Further, the renal cell could be used in toxicological and pharmacological drug screening studies.

There would have been a reasonable expectation of success given Simon et al for teaching that CLC-NKB patients exhibit a chloride transport defect in their renal thick ascending limb and Alberts et al. for teaching how to obtain a cell line from a primary culture.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Claim 38 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gunther et al., (1998, PNAS, USA, 95: 8075-8080) in view of Capecchi (1989, Science, 244: 1288-1292) and Alberts et al.(1994, Molecular Biology of the Cell, Garland Publishing: New York, 3rd ed.).

Gunther et al. teach that ClC-5 provides an electrical shunt that is needed for the efficient proton pumping of the electrogenic H+-ATPase, which is colocalized with ClC-5 (Gunther et al., 1998, PNAS, USA, 95: 8075-8080, Abstract). This idea is supported by the finding that disruption of either the single yeast CLC gene or of a subunit of the V-type H+-ATPase results in a common phenotype (Gunther et al., page 8079, 2nd col., 4th

parag., lines 1-6). While Gunther et al. teach that ClC-5 is provides an electrical shunt needed for proton pumping, Gunther et al. do teach a cell line that expresses ClC-5 that could be used to identify and test substances which are suitable for inhibiting ClC-5.

With regards to providing motivation as to why one would want to generate a cell line that expresses ClC-5, Capecchi teaches that one advantage to carrying out in vitro studies over in vivo studies is that many biological questions can be answered directly and more simply with tissue culture systems (Capecchi, page 1288, 3rd parag., lines 3-4). Certainly, using the cells to screen for compounds that inhibit ClC-5 would be one example of a biological question that could be answered directly and more simply with a tissue culture system.

The generation of a cell line is well known in the art. For example, Alberts et al. teaches that wile most vertebrate cells die after a finite number of divisions in culture, some cells in culture will undergo a genetic change that makes them effectively immortal. Such cells will proliferate indefinitely and can be propagated as a cell line (Alberts et al., page 160, 1st parag. under "Eucaryotic Cell Lines Are a Widely Used Source of Homogenous Cells"). Alberts also teaches that cell lines can be propagated from cancer cells. Cancer cells differ from those prepared from normal cells. For example, cancer cell lines often grown without attaching to a surface and they proliferate to a very much higher density in a culture dish. Similar properties can be experimentally induced in normal cells by transforming them with a tumor-inducing virus or chemical (Alberts et al., page 160, 2nd parag. under "Eucaryotic Cell Lines Are a Widely Used Source of Homogenous Cells").

With regards to expressing ClC-5, the art teaches many ways that ClC-5 can be expressed in a cell line. One way is via transient transfection. Many vectors are available for high levels of expression of exogenous proteins. For example, Invitrogen sells a mammalian expression vector, pcDNA.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to generate a cell line that expresses ClC-5, in order to identify compounds which inhibit ClC-5.

One having ordinary skill in the art would have been motivated to generate a cell line that expresses ClC-5, in order to use the cell in a method of identifying compounds which inhibit ClC-5.

There would have been a reasonable expectation of success given Piwon et al. and Gunther et al for teaching the role ClC-5 has in interacting with the H+/ATP-ase pump, Cappechi teaching why one would prefer to use an in vitro system over an in vivo system, Alberts for teaching how to make a cell line, and Invitrogen for teaching that pcDNA is a vector that can be used in transient expression of mammalian cells.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-

272-2911. The examiner can normally be reached Monday through Thursday and alternate Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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